

Substituted 1- and 2-naphthol Mannich bases

The invention relates to substituted 1- and 2-naphthol Mannich bases, processes for their preparation, medicaments
5 comprising these compounds and the use of these compounds for the preparation of medicaments.

Pain is one of the basic clinical symptoms. There is a worldwide need for effective pain treatments. The urgent
10 need for action for target-orientated treatment of chronic and non-chronic states of pain appropriate for the patient, by which is to be understood successful and satisfactory pain treatment for the patient, is documented in the large number of scientific works which have been published in the
15 field of applied analgesia and basic research in nociception in recent years.

Conventional opioids, such as e.g. morphine, are effective in the treatment of severe to very severe pain. However,
20 they have as undesirable concomitant symptoms, inter alia, respiratory depression, vomiting, sedation, constipation and development of tolerance.

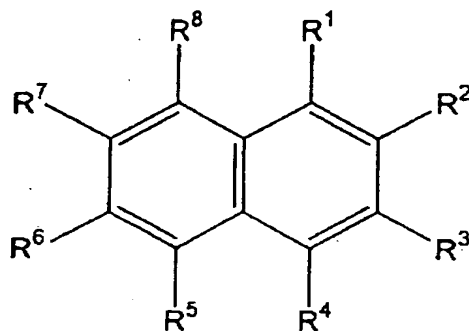
Tramadol hydrochloride - (1RS,2RS)-2-
25 [(dimethylamino)methyl]-1-(3-methoxyphenyl)-cyclohexanol - occupies a special position among analgesics having an action on the central nervous system, since this active compound brings about potent inhibition of pain without the side effects known of opioids (J. Pharmacol. Exptl. Ther.
30 267, 33 (1993)). Research is being conducted worldwide into further pain-inhibiting agents.

The object of the present invention was therefore to provide new compounds which are suitable in particular as active compounds in medicaments.

5 These active compounds should be suitable in particular for pain treatment and for treatment of inflammatory and allergic reactions, drug and/or alcohol abuse, diarrhoea, gastritis, ulcers, cardiovascular diseases, urinary incontinence, depression, states of shock, migraines,
10 narcolepsy, excess weight, asthma, glaucoma and/or hyperkinetic syndrome.

This object is achieved according to the invention by providing substituted 1- and 2-naphthol Mannich bases of
15 the following general formula I which have a pronounced analgesic action and which moreover are suitable for treatment of/combating inflammatory and allergic reactions, drug and/or alcohol abuse, diarrhoea, gastritis, ulcers, cardiovascular diseases, urinary incontinence, depression,
20 states of shock, migraines, narcolepsy, excess weight, asthma, glaucoma and/or hyperkinetic syndrome.

The invention therefore provides substituted 1- and 2-naphthol Mannich bases of the general formula I



wherein

$R^1 = \text{CH}(R^9)\text{N}(R^{10})(R^{11})$ and $R^2 = \text{OR}^{12}$

5 or

$R^1 = \text{OR}^{12}$ and $R^2 = \text{CH}(R^9)\text{N}(R^{10})(R^{11})$,

and in each case the radicals

10

R^3 to R^8 are identical or different and = H, F, Cl, Br, CF_3 , CN, NO_2 , SO_2NH_2 , $\text{SO}_2\text{NHR}^{13}$, NHR^{13} , SR^{15} , OR^{16} , $\text{CO}(\text{OR}^{20})$, $\text{CH}_2\text{CO}(\text{OR}^{21})$, $\text{CO}(\text{R}^{22})$, a C_{1-10} -alkyl, an aryl or a heteroaryl radical or an aryl or heteroaryl radical bonded via a C_{1-6} -alkylene group, preferably = H, F, Cl, Br, SO_2NH_2 , NHR^{13} , $\text{CO}(\text{R}^{22})$, OR^{16} , $\text{CO}(\text{OR}^{20})$, a C_{1-6} -alkyl radical or an aryl radical bonded via a C_{1-2} -alkylene group, particularly preferably H, NHR^{13} , $\text{CO}(\text{R}^{22})$, OR^{16} or $\text{CO}(\text{OR}^{20})$,

15

20 R^9 denotes an aryl radical, a heteroaryl radical or an alkyl radical without an acid proton in the α -position, preferably an unsubstituted phenyl radical or a phenyl radical which is at least monosubstituted by C_{1-4} -alkyl,

C_{1-3} -alkoxy, halogen, CF_3 , CN, O-phenyl or OH, particularly preferably an unsubstituted phenyl radical or a 2-methoxy-phenyl, 3-methoxy-phenyl, 4-methoxy-phenyl, 2-methyl-phenyl, 3-methyl-phenyl, 4-methyl-phenyl, 2-tert-butyl-phenyl, 3-tert-butyl-phenyl, 4-tert-butyl-phenyl, 2-fluoro-phenyl, 3-fluoro-phenyl, 4-fluoro-phenyl, 2-chloro-phenyl, 3-chloro-phenyl, 4-chloro-phenyl, 2-bromo-phenyl, 3-bromo-phenyl, 4-bromo-phenyl, 5-bromo-2-fluoro-phenyl, 2-chloro-4-fluoro-phenyl, 2-chloro-5-fluoro-phenyl, 2-chloro-6-
 5 fluoro-phenyl, 4-bromo-2-fluoro-phenyl, 3-bromo-4-fluoro-phenyl, 3-bromo-2-fluoro-phenyl, 2,3-dichloro-phenyl, 2,4-dichloro-phenyl, 2,5-dichlorophenyl, 3,4-dichloro-phenyl, 2,3-dimethyl-phenyl, 2,4-dimethyl-phenyl, 2,5-dimethylphenyl, 2,3-dimethoxy-phenyl, 2,4-dimethoxy-phenyl,
 10 2,5-dimethoxy-phenyl, 3,4-dimethoxy-phenyl, 3,4,5-trimethoxy-phenyl, 2-trifluoromethyl-phenyl, 3-trifluoromethyl-phenyl or 4-trifluoromethyl-phenyl radical, very particularly preferably an unsubstituted phenyl radical,

20

R^{10} , R^{11} are identical or different and denote a branched or unbranched, saturated or unsaturated, unsubstituted or at least monosubstituted C_{1-6} -alkyl radical or an unsubstituted or at least monosubstituted phenyl, benzyl or phenethyl
 25 radical, preferably a saturated, unsubstituted or at least monosubstituted C_{1-6} -alkyl radical, particularly preferably a CH_3 radical,

or R^{10} and R^{11} together denote $(CH_2)_n$, where n = an integer
 30 from 3 to 6, or $(CH_2)_2O(CH_2)_2$, preferably $(CH_2)_n$, where n = 4 or 5,

$R^{12} = H, COR^{22}$, a C_{1-10} -alkyl, an aryl or a heteroaryl radical or an aryl or heteroaryl radical bonded via a C_{1-6} -alkylene group, preferably $= H$, a C_{1-6} -alkyl radical or an aryl radical bonded via a C_{1-2} -alkylene group,

5

$R^{13} = H, COR^{14}$, a C_{1-10} -alkyl, an aryl or a heteroaryl radical or an aryl or heteroaryl radical bonded via a C_{1-6} -alkylene group, preferably $= H$, a C_{1-6} -alkyl radical or an aryl radical bonded via a C_{1-2} -alkylene group, particularly

10 preferably $= H$,

$R^{14} = H$, a C_{1-10} -alkyl, an aryl or a heteroaryl radical or an aryl or heteroaryl radical bonded via a C_{1-6} -alkylene group, preferably a C_{1-6} -alkyl radical or an aryl radical bonded

15 via a C_{1-2} -alkylene group,

$R^{15} = H$, a C_{1-10} -alkyl, an aryl or a heteroaryl radical or an aryl or heteroaryl radical bonded via a C_{1-6} -alkylene group, preferably a C_{1-6} -alkyl radical or an aryl radical bonded

20 via a C_{1-2} -alkylene group,

$R^{16} = H, CO(R^{17})$, a C_{1-10} -alkyl, an aryl or a heteroaryl radical or an aryl or heteroaryl radical bonded via a C_{1-6} -alkylene group, preferably H , a C_{1-6} -alkyl radical, an aryl radical bonded via a C_{1-2} -alkylene group or $CO(R^{17})$, particularly preferably H or $CO(R^{17})$,

25

$R^{17} = H$, a C_{1-10} -alkyl, an aryl or a heteroaryl radical or an aryl or heteroaryl radical bonded via a C_{1-6} -alkylene group, preferably a C_{1-6} -alkyl radical, an aryl radical bonded via a C_{1-2} -alkylene group or a phenyl radical which is optionally substituted by F, Cl, Br, C_{1-4} -alkyl or C_{1-3} -

30

alkoxy, particularly preferably a phenyl radical which is optionally substituted by F, Cl, Br, C₁₋₄-alkyl or C₁₋₃-alkoxy,

- 5 R¹⁸ = H, a C₁₋₁₀-alkyl, an aryl or a heteroaryl radical or an aryl or heteroaryl radical bonded via a C₁₋₆-alkylene group, preferably a C₁₋₆-alkyl radical, an aryl radical bonded via a C₁₋₂-alkylene group or a phenyl or naphthyl radical which is optionally substituted by F, Cl, Br, C₁₋₄-alkyl or C₁₋₃-
 10 alkoxy, particularly preferably a phenyl radical which is optionally substituted by F, Cl, Br, C₁₋₄-alkyl or C₁₋₃-alkoxy,

- R²⁰ = H, a C₁₋₁₀-alkyl, an aryl or a heteroaryl radical or an
 15 aryl or heteroaryl radical bonded via a C₁₋₆-alkylene group, preferably H, a C₁₋₆-alkyl radical, an aryl radical bonded via a C₁₋₂-alkylene group or a phenyl radical which is optionally substituted by F, Cl, Br, C₁₋₄-alkyl or C₁₋₃-alkoxy, particularly preferably H or a phenyl radical which
 20 is optionally substituted by F, Cl, Br, C₁₋₄-alkyl or C₁₋₃-alkoxy,

- R²¹ = H, a C₁₋₁₀-alkyl, an aryl or a heteroaryl radical or an
 aryl or heteroaryl radical bonded via a C₁₋₆-alkylene group,
 25 preferably = H, a C₁₋₆-alkyl radical or an aryl radical bonded via a C₁₋₂-alkylene group,

- R²² = H, NNNH₂, NHR¹⁸, a C₁₋₁₀-alkyl, an aryl or a heteroaryl
 radical or an aryl or heteroaryl radical bonded via a C₁₋₆-
 30 alkylene group, preferably H, a C₁₋₆-alkyl radical, an aryl radical bonded via a C₁₋₂-alkylene group, NNNH₂, NHR¹⁸ or a phenyl radical which is optionally substituted by F, Cl,

Br, C₁₋₄-alkyl or C₁₋₃-alkoxy, particularly preferably NHNH₂, NHR¹⁸ or a phenyl radical which is optionally substituted by F, Cl, Br, C₁₋₄-alkyl or C₁₋₃-alkoxy, very particularly preferably NHNH₂ or NHR¹⁸,

5

and/or their racemates, enantiomers, diastereomers and/or corresponding bases and/or corresponding salts of physiologically tolerated acids,

10 excluding

the racemates of the compounds in which the radicals R¹ = CH(R⁹)N(R¹⁰)(R¹¹) and R² = OR¹² and in each case

15 the radicals R³ to R⁸ and R¹² = H, the radical R⁹ = phenyl, 2-chlorophenyl, 4-methoxyphenyl, 3-fluorophenyl, 3-chlorophenyl, 3-bromophenyl, 4-bromophenyl, 2-fluorophenyl, 2-bromophenyl, benzo-1,3-dioxole, 4-CH₃OCO-phenyl or 2-methoxyphenyl and the radicals R¹⁰ and R¹¹ together = (CH₂)₅

20

or

25 the radicals R³ to R⁸ and R¹² = H, the radical R⁹ = phenyl, 4-methoxyphenyl, 4-dimethylaminophenyl, 4-hydroxy-2,3-di-tert-butylphenyl, 2,3-dihydrobenzodioxane, 4-nitrophenyl or benzo-1,3-dioxole and the radicals R¹⁰ and R¹¹ together = (CH₂)₂O(CH₂)₂

or

30

the radicals R³ to R⁸ and R¹² = H, the radical R⁹ = 4-methoxyphenyl and the radicals R¹⁰ and R¹¹ together = (CH₂)₄

or

the radical $R^3 = CO(OR^{20})$, the radicals R^4 to R^8 and $R^{12} = H$,
 5 the radical $R^9 =$ phenyl, 4-methoxyphenyl, 4-methylphenyl, 4-nitrophenyl or p-benzaldehyde, the radicals R^{10} and R^{11} together $= (CH_2)_5$ and the radical $R^{20} = CH_3$

or

10

the radicals R^3 to R^8 and $R^{12} = H$, the radical $R^9 =$ phenyl and the two radicals R^{10} and R^{11} each $= CH_3, C_2H_5$ or $n-C_3H_7$

or

15

the radicals R^3 to R^8 and $R^{12} = H$, the radical $R^9 =$ 4-methoxyphenyl or benzo-1,3-dioxole and the radicals R^{10} and R^{11} each $= CH_3$

20 or

the radicals R^3 to $R^5, R^7, R^8, R^{12} = H$, the radical $R^6 = Br$, the radical $R^9 =$ phenyl and the radicals R^{10} and R^{11} together $= (CH_2)_5$

25

or

the radicals R^3 to $R^5, R^7, R^8, R^{12} = H$, the radical $R^6 = Br$, the radical $R^9 =$ 4-hydroxy-3,5-di-tert-butylphenyl and the
 30 radicals R^{10} and R^{11} together $= (CH_2)_2O(CH_2)_2$

or

the radicals R^3 to R^8 and $R^{12} = H$, the radical $R^9 = \text{phenyl}$
and the radicals R^{10} and R^{11} each $= CH_3$ as the hydrochloride

5 or

the radicals R^3 to R^8 and $R^{12} = H$, the radical $R^9 = \text{phenyl or 4-methoxyphenyl}$ and the radicals R^{10} and R^{11} together $= (CH_2)_5$ as the hydrochloride

10

or

the radical $R^3 = CO(OR^{20})$, the radicals R^4 to R^8 and $R^{12} = H$,
the radical $R^9 = \text{phenyl}$, the radicals R^{10} and R^{11} together $=$
15 $(CH_2)_5$ and the radical $R^{20} = CH_3$ as the hydrochloride

or

the radicals R^3 to R^8 and $R^{12} = H$, the radical $R^9 = \text{thiophene}$
and the radicals R^{10} and R^{11} together $= (CH_2)_2O(CH_2)_2$

20

or

the radicals R^3 to $R^8 = H$, the radical $R^{12} = CH_3$, the radical
 $R^9 = \text{thiophene, 4-methoxyphenyl or 3,4-dimethoxyphenyl}$ and
25 the radicals R^{10} and R^{11} together $= (CH_2)_2O(CH_2)_2$

and the enantiomers of the compound of the general formula
I in which $R^1 = CH(R^9)N(R^{10})(R^{11})$ and $R^2 = OR^{12}$ and the
radicals R^3 to R^8 , $R^{12} = H$, $R^9 = \text{phenyl}$ and R^{10} and R^{11}

30 together $= (CH_2)_5$

and

the racemates of the compounds in which the radicals $R^1 = OR^{12}$ and $R^2 = CH(R^9)N(R^{10})(R^{11})$ and in each case the radicals

5 R^3 to R^8 and $R^{12} = H$, the radical $R^9 =$ phenyl, 2-bromophenyl, 3-bromophenyl or 4-bromophenyl and the radicals R^{10} and R^{11} together $= (CH_2)_5$

or

10

R^3 to R^8 and $R^{12} = H$, the radical $R^9 =$ phenyl or 2-nitrophenyl and the radicals R^{10} and R^{11} together $= (CH_2)_2O(CH_2)_2$

15 or

R^3, R^4, R^6, R^8 and $R^{12} = H$, the radicals $R^5, R^7 = CH_3$, the radical $R^9 =$ phenyl or 4-methoxyphenyl and the radicals R^{10} and R^{11} together $= (CH_2)_5$

20

or

R^3 to $R^6, R^8, R^{12} = H$, the radical $R^7 = CH_3$, the radical $R^9 =$ 4-methoxyphenyl or phenyl and the radicals R^{10}, R^{11} together
25 $= (CH_2)_5$

or

R^3 to R^8 and $R^{12} = H$, the radical $R^9 =$ phenyl, the radical R^{10}
30 $= CH_3$ and the radical $R^{11} = C_6H_{11}$ or the radicals R^{10} and R^{11} each $= CH_3$

or

R^3 to R^6 , R^8 , $R^{12} = H$, the radical $R^7 = CH_3$, the radical $R^9 =$
phenyl or 4-methoxyphenyl and the radicals R^{10} and R^{11}
5 together = $(CH_2)_2O(CH_2)_2$

or

R^3 , R^4 , R^6 , R^8 , $R^{12} = H$, the radicals R^5 and $R^7 = CH_3$, the
10 radical $R^9 = 4$ -methoxyphenyl and the radicals R^{10} and R^{11}
together = $(CH_2)_2O(CH_2)_2$

or

15 R^3 to R^8 , $R^{12} = H$, the radical $R^9 =$ phenyl and the radicals
 R^{10} and R^{11} together = $(CH_2)_2O(CH_2)_2$ as the hydrochloride.

Alkyl radicals are preferably understood as hydrocarbon
radicals which are at least monosubstituted by halogen, CN,
20 CF_3 and/or OH, particularly preferably by F, Cl, Br or OH.
If these contain more than one substituent, these
substituents can be identical or different. The alkyl
radicals can be branched, unbranched or cyclic. The alkyl
radicals methyl, ethyl, propyl, 1-methylethyl, butyl, 1-
25 methylpropyl, 2-methylpropyl, 1,1-dimethylpropyl, 1,2-
dimethylpropyl, 2,2-dimethylpropyl, hexyl, 1-methylpentyl,
heptyl, nonyl or decanyl are particularly preferred.

An aryl radical is preferably understood as phenyl or
30 naphthyl radicals which are at least monosubstituted by an
OH, a halogen, preferably F, Br or Cl, a CF_3 , a CN, a C_{1-6} -
alkyl, a C_{1-6} -alkoxy or a phenyl radical. The unsubstituted

or substituted phenyl radicals can also be fused with further rings. The aryl radicals 2-, 3- and 4-bromophenyl, 4-bromo-2-fluorophenyl, 5-bromo-2-fluorophenyl, 3-bromo-4-fluorophenyl, 4-tert-butylphenyl, 2-chloro-4-fluorophenyl, 5 2-chloro-6-fluorophenyl, 4-cyanophenyl, 2,3-dichlorophenyl, 2,4-dichlorophenyl, 2,6-dichlorophenyl, 3,4-dichlorophenyl, 2,3-dimethoxyphenyl, 3,4-dimethoxyphenyl, 2,4-dimethylphenyl, 2,5-dimethylphenyl, 2-, 3- and 4-fluorophenyl, 2-methoxyphenyl, 2-, 3- and 4-methylphenyl, 10 3-phenoxyphenyl, 2- and 4-trifluoromethylphenyl or 3,4,5-trimethoxyphenyl are particularly preferred.

A heteroaryl radical is understood as aromatic compounds which have at least one heteroatom, preferably nitrogen and/or oxygen and/or sulfur, particularly preferably 15 nitrogen and/or oxygen, and which can preferably be substituted by a halogen, a CN, a CF₃ or an OH radical. The heteroaryl radical is very particularly preferably a substituted or unsubstituted thiophene, pyrrolyl or 20 furfuryl radical.

The following substituted 1- and 2-naphthol Mannich bases are particularly preferred:

25 6-(dimethylaminophenylmethyl)-5-hydroxy-naphthalene-1-sulfonic acid amide

4-amino-2-(dimethylaminophenylmethyl)-naphthalen-1-ol

30 4-(dimethylaminophenylmethyl)-3-hydroxy-naphthalene-2-carboxylic acid hydrazide

- 4-(dimethylaminophenylmethyl)-3-hydroxy-naphthalene-2-carboxylic acid methyl ester
- 4-(dimethylaminophenylmethyl)-3-hydroxy-naphthalene-2-carboxylic acid
- 5 4-(dimethylaminophenylmethyl)-3-hydroxy-naphthalene-2-carboxylic acid phenyl ester
- 10 [5-(dimethylaminophenylmethyl)-6-hydroxy-naphthalen-2-yl]-phenylmethanone
- 3-amino-1-(dimethylaminophenylmethyl)-naphthalen-2-ol
- 15 4-(dimethylaminophenylmethyl)-3-hydroxy-naphthalene-2-carboxylic acid (2-methoxy-phenyl)-amide
- 4-(dimethylaminophenylmethyl)-3-hydroxy-naphthalene-2-carboxylic acid o-tolylamide
- 20 4-(dimethylaminophenylmethyl)-3-hydroxy-naphthalene-2-carboxylic acid naphthalen-1-ylamide
- 4-(dimethylaminophenylmethyl)-3-hydroxy-7-methoxy-naphthalene-2-carboxylic acid
- 25 5-(dimethylaminophenylmethyl)-6-hydroxy-naphthalene-2-carboxylic acid
- 30 1-(dimethylaminophenylmethyl)-7-methoxy-naphthalen-2-ol
- 1-(dimethylaminophenylmethyl)-6-methoxy-naphthalen-2-ol

- 5-(dimethylaminophenylmethyl)-6-hydroxy-naphthalene-1-carboxylic acid
- 5 4-(dimethylaminophenylmethyl)-3-hydroxy-7-methoxy-naphthalene-2-carboxylate sodium salt
- 4-chloro-2-(morpholin-4-yl-o-tolylmethyl)-naphthalen-1-ol
- 10 4-chloro-2-(piperidin-1-yl-o-tolylmethyl)-naphthalen-1-ol
- 4-chloro-2-[(2-chlorophenyl)-piperidin-1-yl-methyl]-naphthalen-1-ol
- 15 4-chloro-2-[(2,3-dimethoxyphenyl)-morpholin-4-yl-methyl]-naphthalen-1-ol
- 5-amino-2-[(2-chlorophenyl)-piperidin-1-yl-methyl]-naphthalen-1-ol
- 20 5-amino-2-[(2,3-dimethoxyphenyl)-morpholin-4-yl-methyl]-naphthalen-1-ol
- 3-hydroxy-4-(piperidin-1-yl-o-tolylmethyl)-naphthalene-2-carboxylic acid hydrazide
- 25
- 7-methoxy-1-(morpholin-4-yl-o-tolylmethyl)-naphthalen-2-ol
- 1-[(2-chlorophenyl)-piperidin-1-yl-methyl]-7-methoxy-naphthalen-2-ol
- 30

- 1-[(2,3-dimethoxyphenyl)-morpholin-4-yl-methyl]-7-methoxy-naphthalen-2-ol
- 5 6-bromo-1-[(2-methoxyphenyl)-morpholin-4-yl-methyl]-naphthalen-2-ol
- 6-hydroxy-5-[(2-methoxyphenyl)-morpholin-4-yl-methyl]-naphthalene-1-carboxylic acid
- 10 7-methoxy-1-[(2-methoxyphenyl)-morpholin-4-yl-methyl]-naphthalen-2-ol
- 6-methoxy-1-[(2-methoxyphenyl)-morpholin-4-yl-methyl]-naphthalen-2-ol
- 15 4-chloro-2-[(2-methoxyphenyl)-piperidin-1-yl-methyl]-naphthalen-1-ol
- 6-bromo-1-[(2-methoxyphenyl)-piperidin-1-yl-methyl]-naphthalen-2-ol
- 20 6-methoxy-1-[(2-methoxyphenyl)-piperidin-1-yl-methyl]-naphthalen-2-ol
- 25 7-methoxy-1-[(2-methoxyphenyl)-piperidin-1-yl-methyl]-naphthalen-2-ol
- 5-chloro-2-[dimethylamino-(2-methoxyphenyl)-methyl]-naphthalen-1-ol
- 30 {[1-(4-methoxybenzyloxy)-naphthalen-2-yl]-phenylmethyl}-dimethylamine

{[2-(4-methoxybenzyloxy)-naphthalen-1-yl]-phenylmethyl}-
dimethylamine

5 4-methoxybenzoic acid 1-(dimethylaminophenylmethyl)-
naphthalen-2-yl ester

2-chlorobenzoic acid 1-(dimethylaminophenylmethyl)-
naphthalen-2-yl ester

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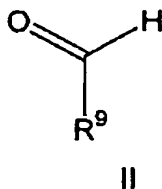
1-(morpholin-4-yl-phenylmethyl)-naphthalen-2-ol

1-(phenylpiperidin-1-yl-methyl)-naphthalen-2-ol

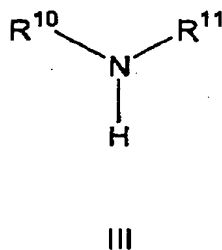
15 2-[(4-fluoro-phenyl)-pyrrolidin-1-yl-methyl]-naphthalen-1-
ol.

The invention also provides processes for the preparation
of substituted 1- and 2-naphthol Mannich bases of the
20 general formula I in which the radical R^{12} represents H and
the radicals R^1 to R^{11} , the radicals R^{13} to R^{18} and the
radicals R^{20} to R^{22} have the meaning according to the general
formula I, which are characterized in that

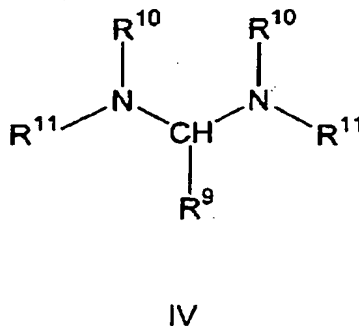
25 aromatic aldehyde compounds, heteroaromatic aldehyde
compounds and/or aliphatic aldehyde compounds of the
general formula II



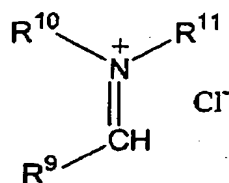
in which R^9 has the meaning according to the general formula I, are reacted in solution, preferably in an organic solvent, particularly preferably in toluene, in the presence of a base, preferably potassium carbonate or boric acid anhydride, preferably at a temperature of -10°C to $+110^\circ\text{C}$, with secondary amines of the general formula III



in which the radicals R^{10} and R^{11} have the meaning according to the general formula I, to give aminal compounds of the general formula IV

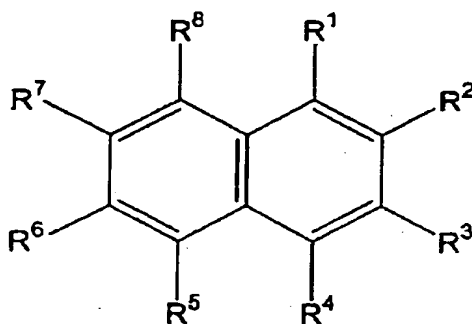


and these aminal compounds of the general formula IV are reacted, without further purification, with an acid chloride, preferably with acetyl chloride, in an absolute solvent, preferably in diethyl ether, to give iminium salts
5 of the general formula V



V

and these iminium salts of the general formula V are reacted, without further purification and in solution,
10 preferably in acetonitrile, with substituted and/or unsubstituted naphthol compounds of the general formula VI

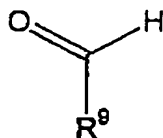


VI

wherein $\text{R}^1 = \text{H}$ and $\text{R}^2 = \text{OH}$ or $\text{R}^1 = \text{OH}$ and $\text{R}^2 = \text{H}$ and the
15 radicals R^3 to R^8 , R^{13} to R^{18} and R^{20} to R^{22} have the meaning according to the general formula I, and the 1- and 2-naphthol compounds of the general formula I obtained in this way in which the radical R^{12} represents H and the radicals R^1 to R^{11} , the radicals R^{13} to R^{18} and the radicals

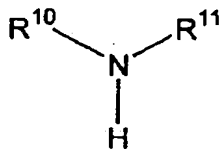
R^{20} to R^{22} have the meaning according to the general formula I are purified by extraction and are isolated by conventional methods.

- 5 The present invention furthermore also provides processes for the preparation of substituted 1- and 2-naphthol Mannich bases of the general formula I in which the radical $R^{12} = COR^{22}$, a C_{1-10} -alkyl, an aryl or a heteroaryl radical or an aryl or heteroaryl radical bonded via a C_{1-6} -alkylene
- 10 group and the radicals R^1 to R^{11} , R^{13} to R^{18} and R^{20} to R^{22} have the meaning according to the general formula I, which are characterized in that
- aromatic aldehyde compounds, heteroaromatic aldehyde compounds and/or aliphatic aldehyde compounds of the
- 15 general formula II



II

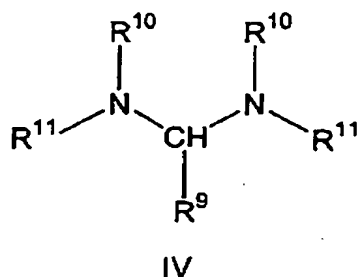
- in which R^9 has the meaning according to the general formula I, are reacted in solution, preferably in an organic
- 20 solvent, particularly preferably in toluene, in the presence of a base, preferably potassium carbonate or boric acid anhydride, preferably at a temperature of -10 to $+110^\circ\text{C}$, with secondary amines of the general formula III



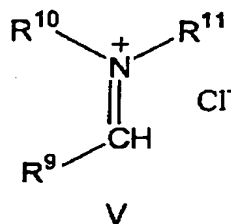
III

in which the radicals R^{10} and R^{11} have the meaning according to the general formula I,
to give ainal compounds of the general formula IV

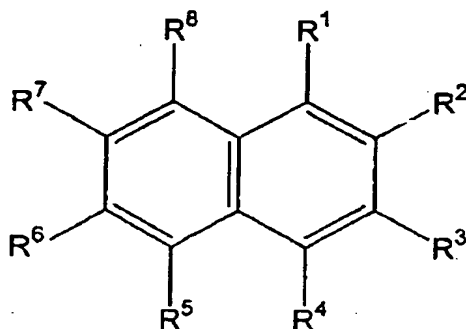
5



and these ainal compounds of the general formula IV are reacted, without further purification, with an acid
10 chloride, preferably with acetyl chloride, in an absolute solvent, preferably in diethyl ether, to give iminium salts of the general formula V



15 and these iminium salts of the general formula V are reacted, without further purification and in solution, preferably in acetonitrile, with substituted and/or unsubstituted naphthol compounds of the general formula VI



VI

wherein $R^1 = H$ and $R^2 = OH$ or $R^1 = OH$ and $R^2 = H$ and in each case the radicals R^3 to R^8 , R^{13} to R^{18} and R^{20} to R^{22} have the meaning according to the general formula I, and the compounds of the general formula VI obtained in this way, wherein $R^1 = CH(R^9)N(R^{10})(R^{11})$ and $R^2 = OH$ or $R^1 = OH$ and $R^2 = CH(R^9)N(R^{10})(R^{11})$ and in each case the radicals R^3 to R^{11} , R^{13} to R^{18} and R^{20} to R^{22} have the meaning according to the general formula I, are reacted in solution, preferably in dimethylformamide, with compounds of the general formula $XR^{12'}$, wherein $X = Cl, Br$ or I , preferably Cl , and $R^{12'}$ represents COR^{22} , a C_{1-10} -alkyl, an aryl or a heteroaryl radical or an aryl or heteroaryl radical bonded via a C_{1-6} -alkylene group, preferably a C_{1-6} -alkyl radical or an aryl radical bonded via a C_{1-2} -alkylene group, in the presence of a base, preferably triethylamine or potassium tert-butylate, preferably at a temperature of 10 to 150°C, and the 1- and 2-naphthol Mannich bases of the general formula I obtained in this way, in which the radical R^{12} represents COR^{22} , a C_{1-10} -alkyl, an aryl or a heteroaryl radical or an aryl or heteroaryl radical bonded via a C_{1-6} -alkylene group, preferably a C_{1-6} -alkyl radical or an aryl radical bonded via a C_{1-2} -alkylene group, and the radicals R^1 to R^{11} , R^{13} to R^{18} and R^{20} to R^{22} have the meaning according to the general

formula I, are purified by filtration, preferably by filtration over a scavenger resin, particularly preferably by filtration over polymer-bonded tris(2-aminoethyl)amine (Novabiochem, Bad Soden) and/or 3-(3-mercaptophenyl)-
5 propane-amidomethylpolystyrene (Argonaut, Muttens, Switzerland).

The synthesis of the substituted 1- and 2-naphthol Mannich bases according to the invention is preferably carried out
10 on an automatic unit from Zymark according to figure 1 and figure 2 as described below.

The substituted 1- and 2-naphthol Mannich bases of the general formula I according to the invention can be
15 converted into their salts in a manner known per se to the expert with physiologically tolerated acids, preferably with hydrochloric acid, hydrobromic acid, sulfuric acid, methanesulfonic acid, formic acid, acetic acid, oxalic acid, succinic acid, tartaric acid, mandelic acid, fumaric
20 acid, lactic acid, citric acid, glutamic acid and/or aspartic acid. The salt formation is preferably carried out in a solvent, particularly preferably in diethyl ether, diisopropyl ether, acetic acid alkyl esters, preferably ethyl acetate, acetone and/or 2-butanone. The salt
25 formation is very particularly preferably carried out with trimethylchlorosilane in methyl ethyl ketone.

The substituted 1- and 2-naphthol Mannich bases of the general formula I according to the invention are
30 toxicologically acceptable and are therefore suitable pharmaceutical active compounds.

The invention therefore also provides medicaments which comprise, as the active compound, at least one substituted 1- and/or 2-naphthol Mannich base of the general formula I and optionally further active compounds and/or auxiliary substances.

The medicament can preferably also comprise a mixture of enantiomers of at least one substituted 1-naphthol Mannich base and/or 2-naphthol Mannich base of the general formula I, the mixture preferably not comprising equimolar amounts of the enantiomers. The relative proportion of one of the enantiomers is particularly preferably 5 to 45 mol%, very particularly preferably 10 to 40 mol%, based on the total mixture of the enantiomers.

The medicaments are preferably employed for treatment of/combating pain and/or inflammatory reactions and/or allergic reactions and/or drug abuse and/or alcohol abuse and/or diarrhoea and/or gastritis and/or ulcers and/or cardiovascular diseases and/or urinary incontinence and/or depression and/or states of shock and/or migraines and/or narcolepsy and/or excess weight and/or asthma and/or glaucoma and/or hyperkinetic syndrome.

The present invention also provides the use of at least one substituted 1- and/or 2-naphthol Mannich base of the general formula I according to the invention for the preparation of a medicament for treatment of/combating pain and/or inflammatory reactions and/or allergic reactions and/or drug abuse and/or alcohol abuse and/or diarrhoea and/or gastritis and/or ulcers and/or cardiovascular diseases and/or urinary incontinence and/or depression

and/or states of shock and/or migraines and/or narcolepsy and/or excess weight and/or asthma and/or glaucoma and/or hyperkinetic syndrome.

5 In addition to at least one substituted 1- and/or 2-naphthol Mannich base of the general formula I, carrier materials, fillers, solvents, diluents, dyestuffs and/or binders are employed for formulating appropriate pharmaceutical formulations. The choice of auxiliary
10 substances depends on whether the medicament is to be administered orally, intravenously, intraperitoneally, intradermally, intramuscularly, intranasally, buccally or locally, for example on infections of the skin, the mucous membranes and the eyes. The formulations in the form of
15 tablets, coated tablets, capsules, granules, drops, juices and syrups are suitable for oral administration, and solutions, suspensions, easily reconstitutable dry formulations and sprays are suitable for parenteral, topical and inhalatory administration.

20 The substituted 1- and 2-naphthol Mannich bases of the general formula I according to the invention in a depot in dissolved form or in a patch, optionally with the addition of agents which promote penetration through the skin, are
25 suitable formulations for percutaneous administration. The compounds of the general formula I according to the invention can be released from oral or percutaneous formulation forms in a delayed manner.

30 The amount of active compound to be administered to the patient varies according to the weight of the patient, the

mode of administration, the indication and the severity of the disease.

Pharmacological studies:

5

1.) In vitro tests

Wide-ranging testing of the 1- and 2-naphthol Mannich bases according to the invention for their activity was carried
10 out by the conventional high throughput screening methods, such as are described in John P. Devlin, High Throughput Screening, 1997, Marcel Dekker Inc. They are introduced herewith as a reference and are therefore part of the disclosure.

15

The action of the 1- and 2-naphthol Mannich bases according to the invention is determined in particular by the affinity for the N-methyl-D-aspartate (NMDA) receptor family, for α -adrenergic receptors and opioid receptors.

20

2.) Analgesia test in the writhing test in mice

The in-depth investigation for analgesic activity was carried out in the phenylquinone-induced writhing in mice
25 (modified by I.C. Hendershot, J. Forsaith, J. Pharmacol. Exp. Ther. 125, 237-240 (1959)). Male NMRI mice weighing 25-30 g were used for this. Groups of 10 animals per substance dose received 0.3 ml/mouse of a 0.02% aqueous solution of phenylquinone (phenylbenzoquinone, Sigma,
30 Deisenhofen; preparation of the solution with the addition of 5% ethanol and storage in a water bath at 45°C) administered intraperitoneally 10 minutes after intravenous

administration of the test substances. The animals were placed individually in observation cages. The number of pain-induced stretching movements (so-called writhing reactions = straightening of the body with stretching of the hind extremities) were counted by means of a push-button counter for 5 - 20 minutes after the administration of phenylquinone. Animals which received only physiological saline solution were also run as a control.

- 10 The substances were tested in the standard dose of 10 mg/kg. The inhibition of the writhing reactions by a substance was calculated according to the following equation:

$$\% \text{ inhibition} = 100 - \left[\frac{\text{writhing reaction of treated animals}}{\text{writhing reaction of control}} \times 100 \right]$$

15

The following examples serve to illustrate the invention, but do not limit the general inventive idea.

Examples:**General synthesis instructions for the preparation of
aminal compounds of the general formula IV:**

5

General synthesis instructions 1:

1.0 equivalent of the particular aromatic, heteroaromatic
or aliphatic aldehyde compound of the general formula II
10 was slowly added dropwise, while stirring at 20°C, to
2.7 equivalents of a 40% solution of the particular
secondary amine with the general formula III. The solution
was then subsequently stirred at a temperature of 80°C for
a further 30 minutes and then cooled to room temperature,
15 and 0.57 equivalent of potassium carbonate was added. Two
phases formed here and were separated from one another, the
aqueous phase being extracted three times with 100 ml ethyl
acetate each time. The combined organic phases were dried
over potassium carbonate and freed from the solvent. The
20 aminal compounds of the general formula IV obtained in this
way were then employed in the subsequent reactions without
further purification.

General synthesis instructions 2:

25

1.6 equivalents of boric acid anhydride were added to a
solution of 1.0 equivalent of the particular aromatic,
heteroaromatic or aliphatic aldehyde compound of the
general formula II in 80 ml absolute toluene. A solution
30 of 2.4 equivalents of a secondary amine of the general
formula III in 85 ml absolute toluene was then added with
vigorous stirring. Starting of the reaction could be seen

by a significant increase in temperature. The reaction solution was then subsequently stirred at a temperature of 45 to 50°C for a further two hours. After cooling to room temperature the excess boric acid anhydride was separated off and the filtrate was freed from the solvent. The amination compounds of the general formula IV obtained in this way were employed in the subsequent reactions without further purification.

10 **General synthesis instructions for the synthesis of iminium salts of the general formula V:**

General synthesis instructions 3:

15 A solution of 1.0 equivalent of acetyl chloride in absolute diethyl ether was slowly added dropwise, while stirring, to 1.0 equivalent of an ice-cooled solution or suspension of the amination compound of the general formula IV prepared in accordance with general synthesis instructions 1 or 2. The reaction mixture was then subsequently stirred overnight at approx. 20°C. A precipitate was formed here, and was filtered off with suction under nitrogen and then dried under an oil pump vacuum. The iminium salts of the general formula V obtained in this way were employed in the subsequent reactions without further purification.

General synthesis instructions for the synthesis of 1- and 2-naphthol Mannich bases of the general formula I:

General synthesis instructions 4:

5

The synthesis of the naphthol Mannich bases according to the invention was carried out on an automatic unit from Zymark according to figure 1 and figure 2:

- 10 Figure 1 here comprises a capper station (no. 1) for closing the reaction tubes, a robot 1 (no. 2) and a robot 2 (no. 3), robot 1 moving the reaction tubes and the corresponding racks and robot 2 pipetting the reagents into the reaction tubes, a temperature-controllable reactor
15 block (no. 4), stirrer blocks (no. 5) and a filtration station (no. 6), in which the reaction solution is filtered.

- Figure 2 also comprises a robot 1 (no. 1) and a robot 2
20 (no. 2), both of which move the glass tubes with the synthesis products to the various stations. The stations are, specifically, a vortexer (no. 3) for thorough mixing of the samples and for metering in solutions or solvents, a spin reactor (no. 4) for thorough mixing of samples, a
25 phase detection station (no. 5) for detection of the phase boundary and phase separation, and a station (no. 6) for drying the synthesis products over salt cartridges.

- For the synthesis, a round-bottomed tube of glass (diameter
30 16 mm, length 125 mm) with a screw-thread was provided manually with a stirrer and closed with a screw-cap with a septum on the capper station (no. 1) according to figure 1.

The tube was placed by robot 1 (no. 2) in the reactor block (no. 4), which was temperature-controlled at 25°C. Robot 2 (no. 3) pipetted in the following reagents in succession:

- 5 1.) 1 ml of a 0.1 M solution of 1- or 2-naphthol or a substituted 1- or 2-naphthol compound of the general formula VI and 14 μ l triethylamine in acetonitrile
- 10 2.) 1.2 ml of a 0.1 M solution of an iminium salt of the general formula V in acetonitrile

The iminium salts were prepared beforehand as described in the following examples. Thereafter, the reaction mixture was stirred at 90°C in one of the stirrer blocks (no. 5) for 960 min. The reaction solution was then filtered at the filtration station (no. 6). The tube was washed twice here with in each case 1 ml methylene chloride and 200 μ l water.

20 The rack with the tubes was then placed manually on an automatic working-up unit according to figure 2. 2 ml water and 2 ml ethyl acetate were added to the reaction mixture there on a vortexer (no. 3).

25 The mixture was brought to a pH of 1 with 1 ml aqueous 5% hydrochloric acid solution. The components were mixed thoroughly in the spin reactor (no. 4) for ten minutes and a clear phase boundary was formed by the slow decrease in the rotational movement. This phase boundary was detected optically on the phase detection station (no. 5) and the aqueous phase was pipetted off. In the next step 2 ml ethyl acetate were added to this and the mixture was

30

brought to a pH of 11 with 1 ml saturated aqueous sodium bicarbonate solution. The components were mixed again thoroughly in the spin reactor (no. 4) for ten minutes and the organic phase was then pipetted off. In the next step
5 1.5 ml ethyl acetate was again added to the aqueous phase. The solution was shaken and centrifuged and the organic phase was pipetted off. The combined organic phases were dried over 2.4 g MgSO_4 (granulated). The solvent was removed in a vacuum centrifuge.

10

General synthesis instructions for the synthesis of alkylated 1- and 2-naphthol Mannich bases of the general formula I:

15 General synthesis instructions 5:

A solution of 1.0 equivalent of 1- and/or 2-naphthol Mannich base of the general formula I where $\text{R}^{12} = \text{H}$ in absolute N,N-dimethylformamide was treated with
20 1.0 equivalent of potassium tert-butyrate for 15 minutes, 1.0 equivalent of alkylating reagent ($\text{R}^{12}\text{-Hal}$) was then added and the mixture was subsequently stirred at approx. 20°C for a further 24 hours. 3.0 equivalents of 3-(3-mercaptophenyl)-propane-amidomethylpolystyrene were then
25 added to this, the components were allowed to react with one another for a further three hours, the PS resin was filtered off and the filtrate was concentrated in vacuo. The residue obtained in this way was taken up in a 1:1 methylene chloride/water mixture, the mixture was stirred
30 for 30 minutes and the phases were separated, the aqueous phase being extracted three times with 20 ml methylene

chloride each time. The combined organic phases were dried over magnesium sulfate and freed from the solvent.

**General synthesis instructions for the synthesis of
5 acylated 1- and 2-naphthol Mannich bases of the general
formula I:**

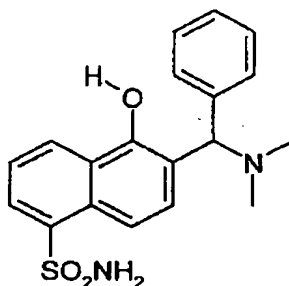
General synthesis instructions 6:

A solution of 1.0 equivalent of 1- and/or 2-naphthol
10 Mannich base of the general formula I where $R^{12} = H$ in
absolute N,N-dimethylformamide was treated with
1.0 equivalent of potassium tert-butyrate for 15 minutes,
1.0 equivalent of acylating reagent (R^{12} -Hal) was then added
and the mixture was subsequently stirred at approx. 20°C
15 for a further 24 hours. 3.0 equivalents of polymer-bonded
tris(2-aminoethyl)amine were then added to this, the
components were allowed to react with one another for a
further three hours, the PS resin was filtered off and the
filtrate was concentrated in vacuo. The residue obtained
20 in this way was taken up in a 1:1 methylene chloride/water
mixture, the mixture was stirred for 30 minutes and the
phases were separated, the aqueous phase being extracted
three times with 20 ml methylene chloride each time. The
combined organic phases were dried over magnesium sulfate
25 and freed from the solvent.

Synthesis of 1- and 2-naphthol Mannich bases of the general formula I:

Example 1:

5



6-(Dimethylaminophenylmethyl)-5-hydroxy-naphthalene-1-sulfonic acid amide

10

1st stage

Benzylidene-dimethyl-ammonium chloride

The reaction of 32.0 ml (0.213 mol) dimethylamine solution and 8.0 ml (0.079 mol) benzaldehyde in accordance with general synthesis instructions 1 and subsequent reaction with 4.7 ml (0.079 mol) acetyl chloride in accordance with general synthesis instructions 3 gave 9.5 g (corresponding to 70.7% of the yield calculated by theory) benzylidene-dimethyl-ammonium chloride.

20

2nd stage

6-(Dimethylaminophenylmethyl)-5-hydroxy-naphthalene-1-sulfonic acid amide

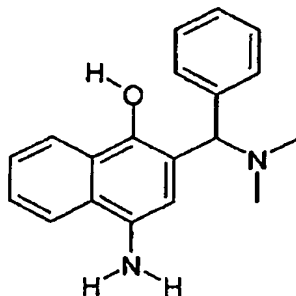
25

The preparation was carried out in accordance with general synthesis instructions 4 from 5-hydroxy-1-

naphthalenesulfonamide and benzylidene-dimethyl-ammonium chloride.

The structure was demonstrated by means of ESI-MS: mass
5 calculated 356.45 g/mol, mass found M+H = 357.3 g/mol.

Example 2:



10

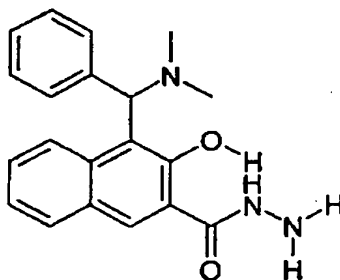
4-Amino-2-(dimethylaminophenylmethyl)-naphthalen-1-ol

The preparation was carried out in accordance with general
synthesis instructions 4 from 1-amino-4-naphthol and
15 benzylidene-dimethyl-ammonium chloride, which had been
prepared in accordance with example 1.

The structure was demonstrated by means of ESI-MS: mass
calculated 292.38 g/mol, mass found M+H = 293.8.

20

Example 3:



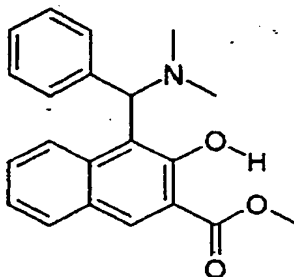
- 5 4-(Dimethylaminophenylmethyl)-3-hydroxy-naphthalene-2-
carboxylic acid hydrazide

The preparation was carried out in accordance with general
synthesis instructions 4 from 2-hydroxy-3-naphthoic acid
10 hydrazide and benzyldiene-dimethyl-ammonium chloride, which
had been prepared in accordance with example 1.

The structure was demonstrated by means of ESI-MS: mass
calculated 335.41 g/mol, mass found M+H = 336.3

15

Example 4:

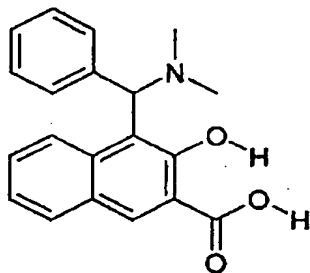


4-(Dimethylaminophenylmethyl)-3-hydroxy-naphthalene-2-carboxylic acid methyl ester

The preparation was carried out in accordance with general synthesis instructions 4 from methyl 3-hydroxy-2-naphthoate and benzylidene-dimethyl-ammonium chloride, which had been prepared in accordance with example 1.

The structure was demonstrated by means of ESI-MS: mass calculated 335.41 g/mol, mass found M+H = 336.5.

Example 5:

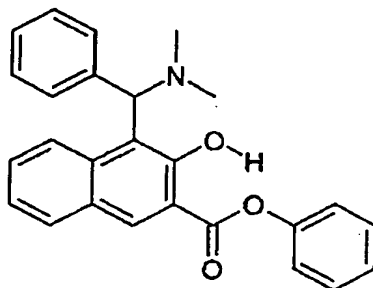


4-(Dimethylaminophenylmethyl)-3-hydroxy-naphthalene-2-carboxylic acid

The preparation was carried out in accordance with general synthesis instructions 4 from 2-hydroxy-3-naphthoic acid and benzylidene-dimethyl-ammonium chloride, which had been prepared in accordance with example 1.

The structure was demonstrated by means of ESI-MS: mass calculated 321.38 g/mol, mass found M+H = 322.2.

Example 6:



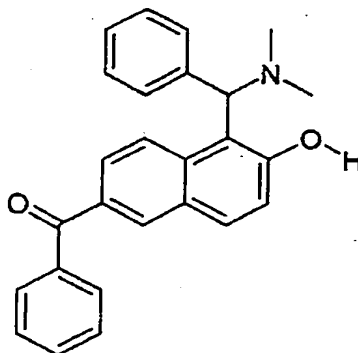
- 5 4-(Dimethylaminophenylmethyl)-3-hydroxy-naphthalene-2-
carboxylic acid phenyl ester

The preparation was carried out in accordance with general
synthesis instructions 4 from 2-hydroxy-3-naphthoic acid
10 phenyl ester and benzyldiene-dimethyl-ammonium chloride,
which had been prepared in accordance with example 1.

The structure was demonstrated by means of ESI-MS: mass
calculated 397.48 g/mol, mass found $M+H = 398.2$.

15

Example 7:

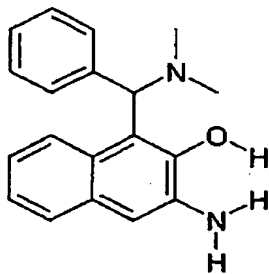


[5-(Dimethylaminophenylmethyl)-6-hydroxy-naphthalen-2-yl]-
phenyl-methanone

The preparation was carried out in accordance with general
5 synthesis instructions 4 from 6-benzoyl-2-naphthol and
benzylidene-dimethyl-ammonium chloride, which had been
prepared in accordance with example 1.

The structure was demonstrated by means of ESI-MS: mass
10 calculated 381.48 g/mol, mass found M+H = 382.2.

Example 8:

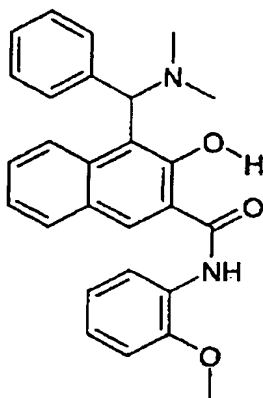


15 3-Amino-1-(dimethylaminophenylmethyl)-naphthalen-2-ol

The preparation was carried out in accordance with general
synthesis instructions 4 from 3-amino-2-naphthol and
benzylidene-dimethyl-ammonium chloride, which had been
20 prepared in accordance with example 1.

The structure was demonstrated by means of ESI-MS: mass
calculated 292.38 g/mol, mass found M+H = 293.3; M+H-NMe₂ =
249.3.

Example 9:

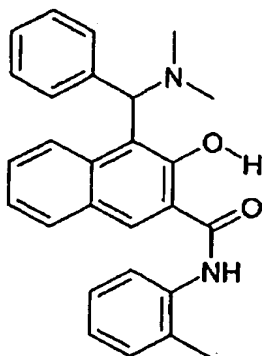


4-(Dimethylaminophenylmethyl)-3-hydroxy-naphthalene-2-
 5 carboxylic acid (2-methoxy-phenyl)-amide

The preparation was carried out in accordance with general
 synthesis instructions 4 from 3-hydroxy-N-(2-
 methoxyphenyl)-2-naphthalenecarboxamide and benzylidene-
 10 dimethyl-ammonium chloride, which had been prepared in
 accordance with example 1.

The structure was demonstrated by means of ESI-MS: mass
 calculated 426.52 g/mol, mass found M+H = 427.0.

Example 10:

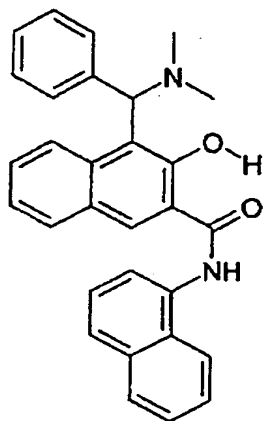


4-(Dimethylaminophenylmethyl)-3-hydroxy-naphthalene-2-
5. carboxylic acid o-tolylamide

The preparation was carried out in accordance with general
synthesis instructions 4 from 3-hydroxy-N-(o-tolyl)-2-
naphthalenecarboxamide and benzylidene-dimethyl-ammonium
10 chloride, which had been prepared in accordance with
example 1.

The structure was demonstrated by means of ESI-MS: mass
calculated 410.52 g/mol, mass found M+H = 412.0.

Example 11:

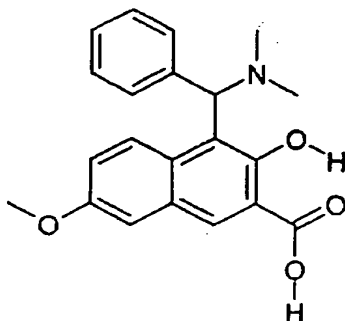


5 4-(Dimethylaminophenylmethyl)-3-hydroxy-naphthalene-2-
carboxylic acid naphthalen-1-ylamide

The preparation was carried out in accordance with general
synthesis instructions 4 from 3-hydroxy-N-(naphthyl)-2-
10 naphthalenecarboxamide and benzylidene-dimethyl-ammonium
chloride, which had been prepared in accordance with
example 1.

The structure was demonstrated by means of ESI-MS: mass
15 calculated 446.55 g/mol, mass found $M+H = 447.8$.

Example 12:

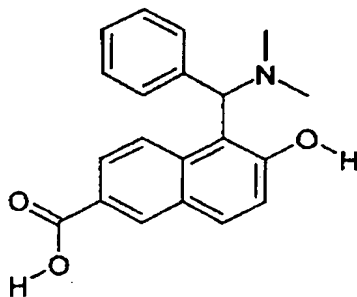


4-(Dimethylaminophenylmethyl)-3-hydroxy-7-methoxy-naphthalene-2-carboxylic acid

The preparation was carried out in accordance with general synthesis instructions 4 from 3-hydroxy-7-methoxy-2-naphthoic acid and benzyldiene-dimethyl-ammonium chloride, which had been prepared in accordance with example 1.

The structure was demonstrated by means of ESI-MS: mass calculated 351.41 g/mol, mass found M+H = 352.3.

Example 13:



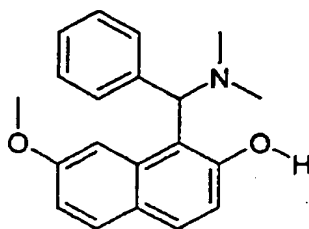
15

5-(Dimethylaminophenylmethyl)-6-hydroxy-naphthalene-2-carboxylic acid

The preparation was carried out in accordance with general synthesis instructions 4 from 6-hydroxy-2-naphthoic acid and benzyldiene-dimethyl-ammonium chloride, which had been prepared in accordance with example 1.

The structure was demonstrated by means of ESI-MS: mass calculated 321.38 g/mol, mass found M+H = 322.1.

Example 14:



1-(Dimethylaminophenylmethyl)-7-methoxynaphthalen-2-ol

5

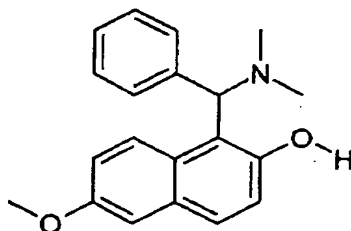
The preparation was carried out in accordance with general synthesis instructions 4 from 7-methoxy-2-naphthol and benzyldiene-dimethyl-ammonium chloride, which had been prepared in accordance with example 1.

10

The structure was demonstrated by means of ESI-MS: mass calculated 307.36 g/mol, mass found M+H = 308.4.

Example 15:

15

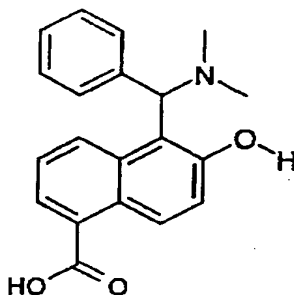


1-(Dimethylaminophenylmethyl)-6-methoxynaphthalen-2-ol

20 The preparation was carried out in accordance with general synthesis instructions 4 from 6-methoxy-2-naphthol and benzyldiene-dimethyl-ammonium chloride, which had been prepared in accordance with example 1.

The structure was demonstrated by means of ESI-MS: mass calculated 307.4 g/mol, mass found $M:H = 308.3$.

5 Example 16:

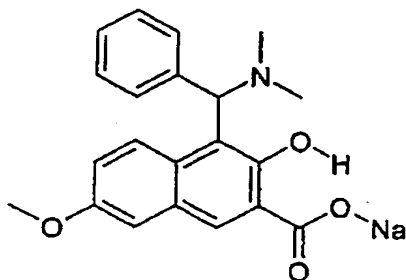


5-(Dimethylaminophenylmethyl)-6-hydroxynaphthalene-1-
10 carboxylic acid

The preparation was carried out in accordance with general synthesis instructions 4 from 6-hydroxy-1-naphthoic acid and benzylidene-dimethyl-ammonium chloride, which had been
15 prepared in accordance with example 1.

The structure was demonstrated by means of ESI-MS: mass calculated 321.38 g/mol, mass found $M+H = 322.2$.

Example 17:



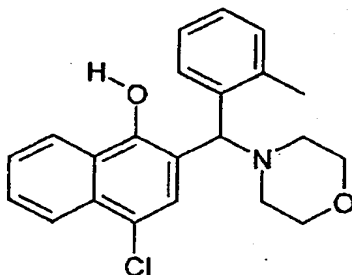
4-(Dimethylaminophenylmethyl)-3-hydroxy-7-
5 methoxynaphthalene-carboxylate sodium salt

The preparation was carried out in accordance with general
synthesis instructions 4 from the sodium salt of 3-hydroxy-
7-methoxy-2-naphthoic acid and benzylidene-dimethyl-
10 ammonium chloride, which had been prepared in accordance
with example 1.

The structure was demonstrated by means of ESI-MS: mass
calculated 373.39 g/mol, mass found $M+H-Na = 352.0$.

15

Example 18:



4-Chloro-2-(morpholin-4-yl-o-tolylmethyl)-naphthalen-1-ol

1st stage

4-(2-Methyl-benzylidene)-morpholin-4-ium chloride

5

The reaction of 8.5 g (0.100 mol) morpholine and 7.0 g (0.050 mol) 2-methoxybenzaldehyde in accordance with general synthesis instructions 2 and subsequent reaction with 3.9 g (0.050 mol) acetyl chloride in accordance with
 10 general synthesis instructions 3 gave 7.1 g (corresponding to 58% of the yield calculated by theory) 4-(2-methyl-benzylidene)-morpholin-4-ium chloride.

2nd stage

15 4-Chloro-2-(morpholin-4-yl-o-tolylmethyl)-naphthalen-1-ol

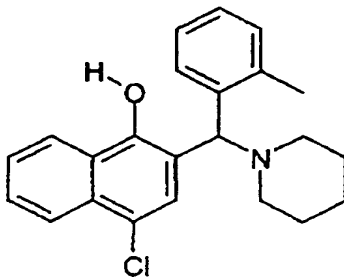
The preparation was carried out in accordance with general synthesis instructions 4 from 4-chloro-1-naphthol and 4-(2-methyl-benzylidene)-morpholin-4-ium chloride.

20

The structure was demonstrated by means of ESI-MS: mass calculated 367.88 g/mol, mass found $M+H = 368.1$.

Example 19:

25



4-Chloro-2-(piperidin-1-yl-o-tolylmethyl)-naphthalen-1-ol

1st stage

1-(2-Methyl-benzylidene)-piperidinium chloride

5

The reaction of 9.5 ml (0.096 mol) piperidine and 4.7 ml (0.040 mol) 2-methylbenzaldehyde in accordance with general synthesis instructions 2 and subsequent reaction with 2.4 ml (0.040 mol) acetyl chloride in accordance with general synthesis instructions 3 gave 5.8 g (corresponding to 65% of the yield calculated by theory) 1-(2-methyl-benzylidene)-piperidinium chloride.

2nd stage

15 4-Chloro-2-(piperidin-1-yl-o-tolylmethyl)-naphthalen-1-ol

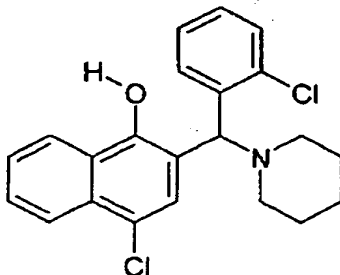
The preparation was carried out in accordance with general synthesis instructions 4 from 1-(2-methyl-benzylidene)-piperidinium chloride and 4-chloro-1-naphthol.

20

The structure was demonstrated by means of ESI-MS: mass calculated 365.91 g/mol, mass found $M+H = 366.2$.

Example 20:

25



4-Chloro-2-[(2-chlorophenyl)-piperidin-1-yl-methyl]-
naphthalen-1-ol

1st stage

5 1-(2-Chloro-benzylidene)-piperidinium chloride

The reaction of 8.5 g (0.100 mol) piperidine and 7.0 g
(0.050 mol) 2-chlorobenzaldehyde in accordance with general
synthesis instructions 2 and subsequent reaction with 3.9 g
10 (0.050 mol) acetyl chloride in accordance with general
synthesis instructions 3 gave 7.1 g (corresponding to 58%
of the yield calculated by theory) 1-(2-methyl-
benzylidene)-piperidinium chloride.

15 2nd stage

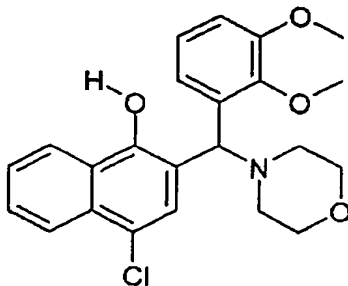
4-Chloro-2-[(2-chlorophenyl)-piperidin-1-yl-methyl]-
naphthalen-1-ol

The preparation was carried out in accordance with general
20 synthesis instructions 4 from 1-(2-chloro-benzylidene)-
piperidinium chloride and 4-chloro-1-naphthol.

The structure was demonstrated by means of ESI-MS: mass
calculated 386.32 g/mol, mass found M+H = 386.1.

25

Example 21:



4-Chloro-2-[(2,3-dimethoxyphenyl)-morpholin-4-yl-methyl]-
naphthalen-1-ol

1st stage

5 4-(2,3-Dimethoxy-benzylidene)-morpholin-4-ium chloride

The reaction of 7.3 ml (0.084 mol) morpholine and 5.8 g
(0.035 mol) 2,3-dimethoxybenzaldehyde in accordance with
general synthesis instructions 2 and subsequent reaction
10 with 2.1 ml (0.035 mol) acetyl chloride in accordance with
general synthesis instructions 3 gave 5.6 g (corresponding
to 59% of the yield calculated by theory) 4-(2,3-dimethoxy-
benzylidene)-morpholin-4-ium chloride.

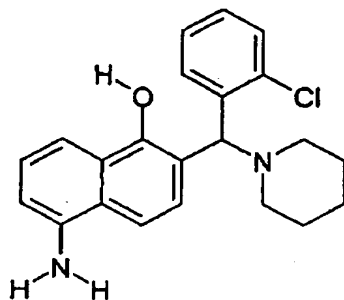
15 2nd stage

4-Chloro-2-[(2,3-dimethoxyphenyl)-morpholin-4-yl-methyl]-
naphthalen-1-ol

The preparation was carried out in accordance with general
20 synthesis instructions 4 from 4-(2,3-dimethoxy-
benzylidene)-morpholin-4-ium chloride and 4-chloro-1-
naphthol.

The structure was demonstrated by means of ESI-MS: mass
25 calculated 413.91 g/mol, mass found M+H = 414.0.

Example 22:

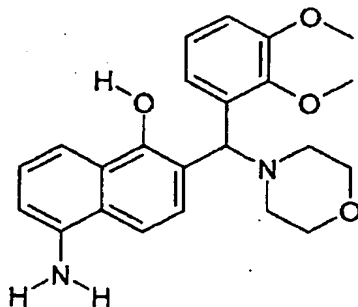


5-Amino-2-[(2-chlorophenyl)-piperidin-1-yl-methyl]-
5 naphthalen-1-ol

The preparation was carried out in accordance with general
synthesis instructions 4 from 5-amino-1-naphthol and 1-(2-
chloro-benzylidene)-piperidinium chloride, which had been
10 prepared in accordance with example 20.

The structure was demonstrated by means of ESI-MS: mass
calculated 366.89 g/mol, mass found $M+H = 367.4$.

15 Example 23:

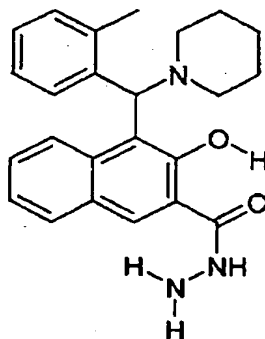


5-Amino-2-[(2,3-dimethoxyphenyl)-morpholin-4-yl-methyl]-naphthalen-1-ol

The preparation was carried out in accordance with general synthesis instructions 4 from 5-amino-1-naphthol and 4-(2,3-dimethoxy-benzylidene)-morpholin-4-ium chloride, which had been prepared in accordance with example 21.

The structure was demonstrated by means of ESI-MS: mass calculated 394.47 g/mol, mass found M+H = 395.1.

Example 24:



3-Hydroxy-4-(piperidin-1-yl-o-tolylmethyl)-naphthalene-2-carboxylic acid hydrazide

1st stage

1-(2-Methyl-benzylidene)-piperidinium chloride

20

The reaction of 9.5 ml (0.096 mol) piperidine and 4.7 ml (0.040 mol) 2-methylbenzaldehyde in accordance with general synthesis instructions 2 and subsequent reaction with 2.4 ml (0.040 mol) acetyl chloride in accordance with general synthesis instructions 3 gave 5.8 g (corresponding

to 65% of the yield calculated by theory) 1-(2-methyl-benzylidene)-piperidinium chloride.

2nd stage

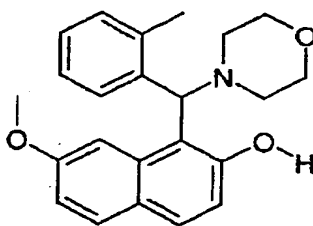
- 5 3-Hydroxy-4-(piperidin-1-yl-o-tolylmethyl)-naphthalene-2-carboxylic acid hydrazide

The preparation was carried out in accordance with general synthesis instructions 4 from 1-(2-methyl-benzylidene)-piperidinium chloride and 2-hydroxy-3-naphthoic acid hydrazide.

The structure was demonstrated by means of ESI-MS: mass calculated 389.5 g/mol, mass found M+H = 388.5.

15

Example 25:



7-Methoxy-1-(morpholin-4-yl-o-tolylmethyl)-naphthalen-2-ol

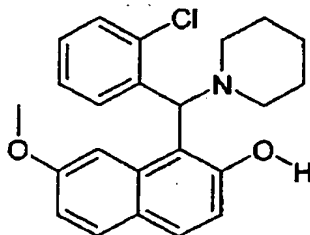
20

The preparation was carried out in accordance with general synthesis instructions 4 from 7-methoxy-2-naphthol and 4-(2-methyl-benzylidene)-morpholin-4-ium chloride, which had been prepared in accordance with example 18.

25

The structure was demonstrated by means of ESI-MS: mass calculated 389.41 g/mol, mass found M+H = 389.5.

Example 26:

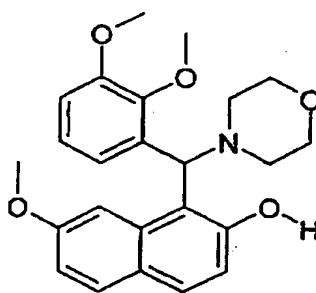


1-[(2-Chlorophenyl)-piperidin-1-yl-methyl]-7-methoxy-
5 naphthalen-2-ol

The preparation was carried out in accordance with general
synthesis instructions 4 from 7-methoxy-2-naphthol and 1-
(2-chloro-benzylidene)-piperidinium chloride, which had
10 been prepared in accordance with example 20.

The structure was demonstrated by means of ESI-MS: mass
calculated 381.91 g/mol, mass found $M+H = 382.2$.

15 Example 27:



1-[(2,3-Dimethoxyphenyl)-morpholin-4-yl-methyl]-7-methoxy-
naphthalen-2-ol

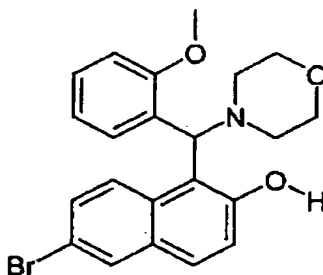
20

The preparation was carried out in accordance with general
synthesis instructions 4 from 7-methoxy-2-naphthol and 4-

(2,3-dimethoxy-benzylidene)-morpholin-4-ium chloride, which had been prepared in accordance with example 21.

The structure was demonstrated by means of ESI-MS: mass
5 calculated 409.49 g/mol, mass found M+H = 409.9.

Example 28:



10

6-Bromo-1-[(2-methoxyphenyl)-morpholin-4-yl-methyl]-
naphthalen-2-ol

1st stage

15 4-(2-Methoxy-benzylidene)-morpholin-4-ium chloride

The reaction of 18.8 ml (0.216 mol) morpholine and 12.4 g
(0.09 mol) 2-methoxybenzaldehyde in accordance with general
synthesis instructions 2 and subsequent reaction with
20 5.3 ml (0.110 mol) acetyl chloride in accordance with
general synthesis instructions 3 gave 7.61 g (corresponding
to 38% of the yield calculated by theory) 4-(2-methoxy-
benzylidene)-morpholin-4-ium chloride.

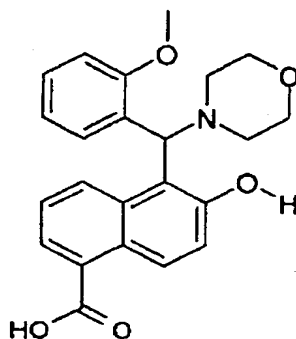
2nd stage

6-Bromo-1-[(2-methoxyphenyl)-morpholin-4-yl-methyl]-
naphthalen-2-ol

- 5 The preparation was carried out in accordance with general
synthesis instructions 4 from 4-(2-methoxy-benzylidene)-
morpholin-4-ium chloride and 6-bromo-2-naphthol.

The structure was demonstrated by means of ESI-MS: mass
10 calculated 428.33 g/mol, mass found M+H = 428.1/430.0.

Example 29:

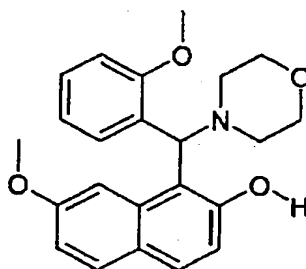


- 15 6-Hydroxy-5-[(2-methoxyphenyl)-morpholin-4-yl-methyl]-
naphthalene-1-carboxylic acid

The preparation was carried out in accordance with general
synthesis instructions 4 from 6-hydroxy-1-naphthoic acid
20 and 4-(2-methoxy-benzylidene)-morpholin-4-ium chloride,
which had been prepared in accordance with example 28.

The structure was demonstrated by means of ESI-MS: mass
calculated 393.44 g/mol, mass found M+H = 394.1.

Example 30:

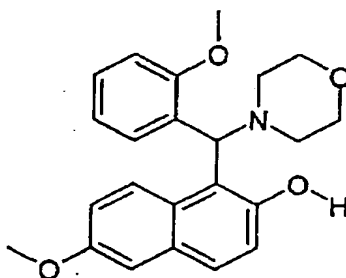


7-Methoxy-1-[(2-methoxyphenyl)-morpholin-4-yl-methyl]-
 5 naphthalen-2-ol

The preparation was carried out in accordance with general
 synthesis instructions 4 from 7-methoxy-2-naphthol and
 4-(2-methoxy-benzylidene)-morpholin-4-ium chloride, which
 10 had been prepared in accordance with example 28.

The structure was demonstrated by means of ESI-MS: mass
 calculated 379.46 g/mol, mass found M+H = 380.2.

15 Example 31:



6-Methoxy-1-[(2-methoxyphenyl)-morpholin-4-yl-methyl]-
 naphthalen-2-ol

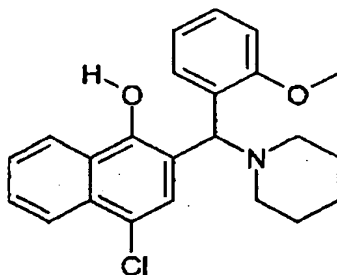
20

The preparation was carried out in accordance with general
 synthesis instructions 4 from 6-methoxy-2-naphthol and 4-

(2-methoxy-benzylidene)-morpholin-4-ium chloride, which had been prepared in accordance with example 28.

The structure was demonstrated by means of ESI-MS: mass
5 calculated 379.46 g/mol, mass found M+H = 380.1.

Example 32:



10

4-Chloro-2-[(2-methoxyphenyl)-piperidin-1-yl-methyl]-
naphthalen-1-ol

1st stage

15 1-(2-Methoxy-benzylidene)-piperidinium chloride

The reaction of 18.4 g (0.216 mol) piperidine and 25.9 g
(0.090 mol) 2-methoxybenzaldehyde in accordance with
general synthesis instructions 2 and subsequent reaction
20 with 5.3 ml (0.11 mol) acetyl chloride in accordance with
general synthesis instructions 3 gave 13.4 g (corresponding
to 62% of the yield calculated by theory) 1-(2-methoxy-
benzylidene)-piperidinium chloride.

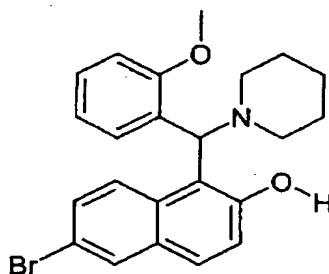
2nd stage

4-Chloro-2-[(2-methoxyphenyl)-piperidin-1-yl-methyl]-
naphthalen-1-ol

- 5 The preparation was carried out in accordance with general synthesis instructions 4 from 1-(2-methoxy-benzylidene)-piperidinium chloride and 4-chloro-1-naphthol.

The structure was demonstrated by means of ESI-MS: mass
10 calculated 381.91 g/mol, mass found M+H-piperidine = 297.2.

Example 33:



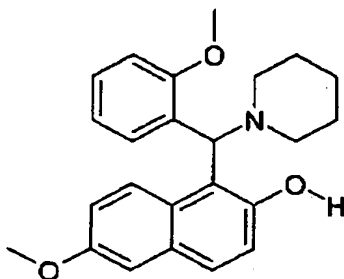
15

6-Bromo-1-[(2-methoxyphenyl)-piperidin-1-yl-methyl]-
naphthalen-2-ol

- The preparation was carried out in accordance with general
20 synthesis instructions 4 from 6-bromo-2-naphthol and 1-(2-methoxy-benzylidene)-piperidinium chloride, which had been prepared in accordance with example 32.

The structure was demonstrated by means of ESI-MS: mass
25 calculated 426.36 g/mol, mass found M+H = 426.1/428.2.

Example 34:

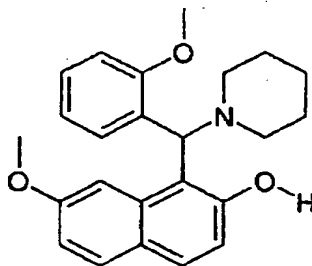


6-Methoxy-1-[(2-methoxyphenyl)-piperidin-1-yl-methyl]-
 5 naphthalen-2-ol

The preparation was carried out in accordance with general
 synthesis instructions 4 from 6-methoxy-2-naphthol and 1-
 (2-methoxy-benzylidene)-piperidinium chloride, which had
 10 been prepared in accordance with example 32.

The structure was demonstrated by means of ESI-MS: mass
 calculated 377.49 g/mol, mass found M+H = 378.2.

15 Example 35:



7-Methoxy-1-[(2-methoxyphenyl)-piperidin-1-yl-methyl]-
 naphthalen-2-ol

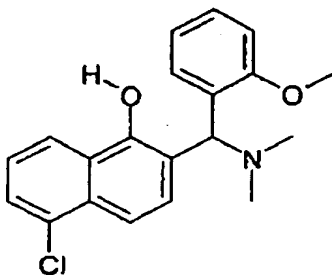
20

The preparation was carried out in accordance with general
 synthesis instructions 4 from 7-methoxy-2-naphthol and 1-

(2-methoxy-benzylidene)-piperidinium chloride, which had been prepared in accordance with example 32.

The structure was demonstrated by means of ESI-MS: mass
5 calculated 377.49 g/mol, mass found M+H = 378.2.

Example 36:



10

5-Chloro-2-[dimethylamino-(2-methoxyphenyl)-methyl]-
naphthalen-1-ol

1st stage

15 (2-Methoxy-benzylidene)-dimethyl-ammonium chloride

The reaction of 17.0 ml (0.135 mol) dimethylamine solution
and 6.8 ml (0.050 mol) 2-methoxybenzaldehyde in accordance
with general synthesis instructions 1 and subsequent
20 reaction with 3.0 ml (0.050 mol) acetyl chloride in
accordance with general synthesis instructions 3 gave 4.8 g
(corresponding to 48% of the yield calculated by theory)
(2-methoxy-benzylidene)-dimethyl-ammonium chloride.

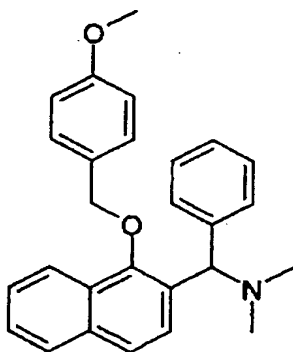
2nd stage

5-Chloro-2-[dimethylamino-(2-methoxyphenyl)-methyl]-
naphthalen-1-ol

- 5 The preparation was carried out in accordance with general synthesis instructions 4 from (2-methoxy-benzylidene)-dimethyl-ammonium chloride and 5-chloro-1-naphthol.

The structure was demonstrated by means of ESI-MS: mass
10 calculated 341.84 g/mol, mass found $M+H-NMe_2 = 297.2$.

Example 37:



15

{[1-(4-Methoxy-benzyloxy)-naphthalen-2-yl]-phenylmethyl}-
dimethylamine

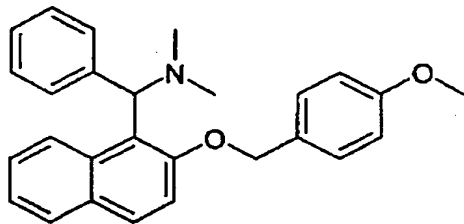
The preparation was carried out in accordance with general
20 synthesis instructions 4 and 5 from 1-naphthol and
benzylidene-dimethyl-ammonium chloride and 4-methoxybenzyl
chloride.

The structure was demonstrated by means of ^{13}C -NMR: $\delta =$
25 159.59; 151.92; 143.30; 134.03; 132.03; 129.22 (C_q); 129.76;

128.38; 128.07; 127.99; 126.87; 125.84; 125.74; 124.61;
122.40; 114.10 (C_t); 75.85 (C_s); 69.46; 55.38; 44.82 (C_p).

Example 38:

5



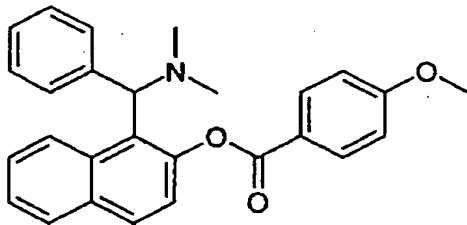
{[2-(4-Methoxybenzyloxy)-naphthalen-1-yl]-phenylmethyl}-
dimethylamine

10

The preparation was carried out in accordance with general
synthesis instructions 4 and 5 from 2-naphthol,
benzylidene-dimethyl-ammonium chloride and 4-methoxybenzyl
chloride. The structure was demonstrated by means of ESI-

15 MS: mass calculated 397.52 g/mol, mass found $M+H = 398.0$.

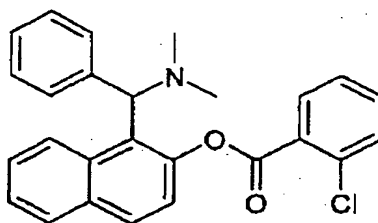
Example 39:



4-Methoxybenzoic acid 1-(dimethylaminophenylmethyl)-
naphthalen-2-yl ester

The preparation was carried out in accordance with general
5 synthesis instructions 4 and 6 from 2-naphthol,
benzylidene-dimethyl-ammonium chloride and 4-methoxybenzoyl
chloride. The structure was demonstrated by means of ESI-
MS: mass calculated 411.51 g/mol, mass found M+H = 412.0.

10 Example 40:

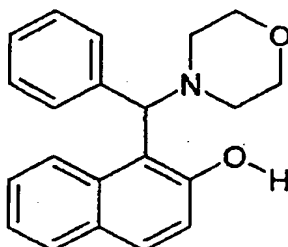


2-Chlorobenzoic acid 1-(dimethylaminophenylmethyl)-
15 naphthalen-2-yl ester

The preparation was carried out in accordance with general
synthesis instructions 4 and 6 from 2-naphthol,
benzylidene-dimethyl-ammonium chloride and 2-chlorobenzoyl
20 chloride.

The structure was demonstrated by means of ESI-MS: mass
calculated 415.92 g/mol, mass found M+H = 416.0.

Example 41:



5 1-(Morpholin-4-yl-phenylmethyl)-naphthalen-2-ol

1st stage

4-Benzylidene-morpholin-4-ium chloride

- 10 The reaction of 17.9 ml (0.200 mol) morpholine and 10.1 ml (0.100 mol) benzaldehyde in accordance with general synthesis instructions 2 and subsequent reaction with 6.0 ml (0.100 mol) acetyl chloride in accordance with general synthesis instructions 3 gave 10.1 g (corresponding to 48% of the yield calculated by theory) 4-benzylidene-morpholin-4-ium chloride.

2nd stage

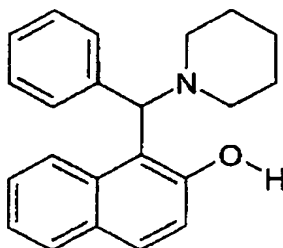
1-(Morpholin-4-yl-phenyl-methyl)-naphthalen-2-ol

20

The preparation was carried out in accordance with general synthesis instructions 4 from 4-benzylidene-morpholin-4-ium chloride and 2-naphthol.

- 25 The structure was demonstrated by means of ESI-MS: mass calculated 319.41 g/mol, mass found $M+H = 320.1$ g/mol.

Example 42:



5 1-(Phenylpiperidin-1-yl-methyl)-naphthalen-2-ol

1st stage

1-Benzylidene-piperidinium chloride

10 The reaction of 19.8 ml (0.200 mol) piperidine and 10.1 ml (0.100 mol) benzaldehyde in accordance with general synthesis instructions 2 and subsequent reaction with 6.0 ml (0.100 mol) acetyl chloride in accordance with general synthesis instructions 3 gave 11.7 g (corresponding

15 to 56% of the yield calculated by theory) 1-benzylidene-piperidinium chloride.

2nd stage

1-(Phenylpiperidin-1-yl-methyl)-naphthalen-2-ol

20

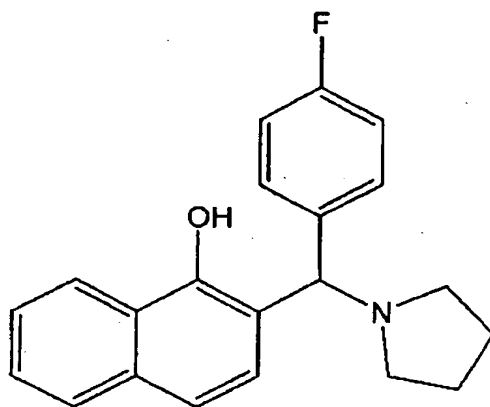
The preparation was carried out in accordance with general synthesis instructions 4 from 1-benzylidene-piperidinium chloride and 2-naphthol.

25 The structure was demonstrated by means of ESI-MS: mass calculated 317.43 g/mol, mass found M+H = 318.3 g/mol.

Example 43:

2-[(4-Fluoro-phenyl)-pyrrolidin-1-yl-methyl]-naphthalen-1-ol

5



The preparation was carried out in accordance with general synthesis instructions 4 from 1-naphthol and (4-fluoro-
10 benzylidene)-pyrrolidinium chloride, which had been prepared in accordance with example 41 from 4-fluorobenzaldehyde and pyrrolidine.

The structure was demonstrated by means of ESI-MS: mass
15 calculated 321.4 g/mol, mass found M+H = 322.1 g/mol, M-pyrrolidine 251.3 g/mol.

Pharmacological studies

1.) In vitro tests

- 5 The 1- and 2-naphthol Mannich bases according to the invention were tested for their activity as described above.

2.) Analgesia test in the writhing test in mice

10

The in-depth investigation for analgesic activity was carried out in the phenylquinone-induced writhing in mice as described above.

- 15 The compounds according to the invention investigated showed an analgesic action.

The results of selected writhing investigations are summarized in the following table 1.

20

Table 1: Analgesia test in the writhing test in mice

Example no.	Inhibition of the writhing reaction in %
37	40
38	81
39	21
40	48
41	30
42	92